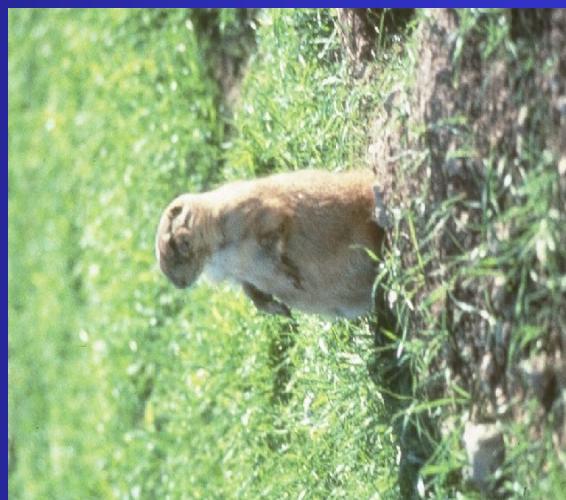
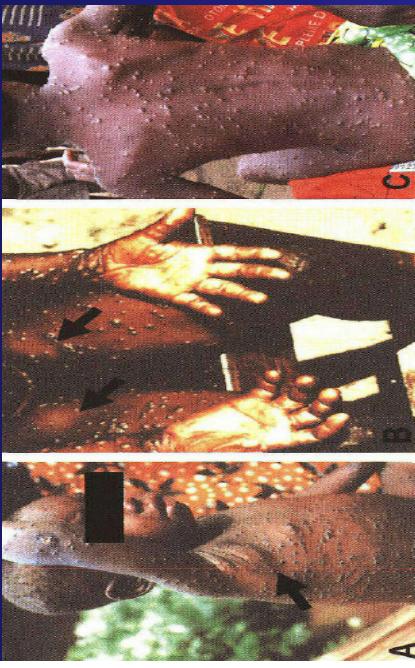
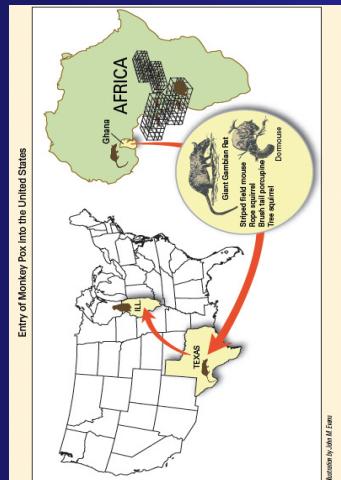
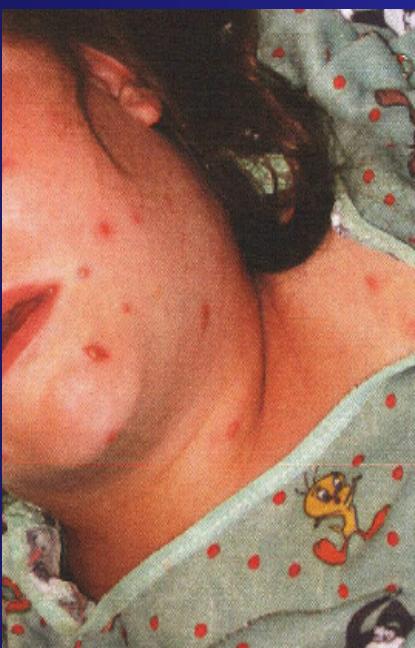


Monkeypox Historical Perspective and Overview 2006

One Medicine Symposium
December 6-7, 2006
Research Triangle Park

C. Gregory Smith, MD, MPH
General Communicable Disease Control Branch
Epidemiology Section
North Carolina Division of Public Health

Human Monkeypox



Black-footed Ferrets

Prairie Dogs

African Rodents

Poxviruses by Genus

- Orthopoxvirus
 - Cowpox, Monkeypox, Vaccinia, Variola (Smallpox), Camelpox
- Yatapoxvirus
 - Tanapox, Yatapox (non-human primates, humans incidentally)
- Parapoxvirus
 - Orf, Pseudocowpox, Bovine Papular Stomatitis, Sealpox
- Molluscipoxvirus
 - Molluscipox (*Molluscum contagiosum*) human & nh primates
- Avipoxvirus (Fowlpox-birds)
- Capripoxvirus (Sheep pox-sheep, goats, cows)
- Leporipoxvirus (Myxoma-squirrels, rodents, rabbits)
- Suipoxvirus (Swinepox)

Orthopoxviruses

| Species | Host | Primary Reservoir | Geographic Region | Mode of Transmission | Protection by Vaccinia Vaccination |
|---------------------------------------|------------------------------|--------------------------------------|--|---|------------------------------------|
| Vaccinia (? Extinct horsepoxvirus) | Humans | Unknown | ?? Indian Subcontinent Buffulopoxvirus | Direct contact | |
| Cowpox (CPV) | Humans, cats, cattle rodents | Rodents | Europe, Africa, Asia | Direct contact | Yes |
| Variola Smallpox (SPXV) | Humans | Humans No known animal reservoirs | US, Russia (laboratories) Eradicated 1980 WHO | Direct contact, Respiratory droplets | Yes |
| Monkeypox (MPXV) | Humans, monkeys, rodents | Rodents | Central and West Africa | Direct contact, Respiratory droplets | Yes |
| Camelpox (CMPV) | Camels, ? Humans | Camels | Africa, Asia | Direct contact | Probably |

Monkeypox Virus (MPXV)

Family Poxviridae

Subfamily Chordopoxvirinae

Genus *Orthopoxvirus*

MPX Patient-Electronmicrograph of Skin Biopsy-Mashfield Clinic, Marshfield, WI

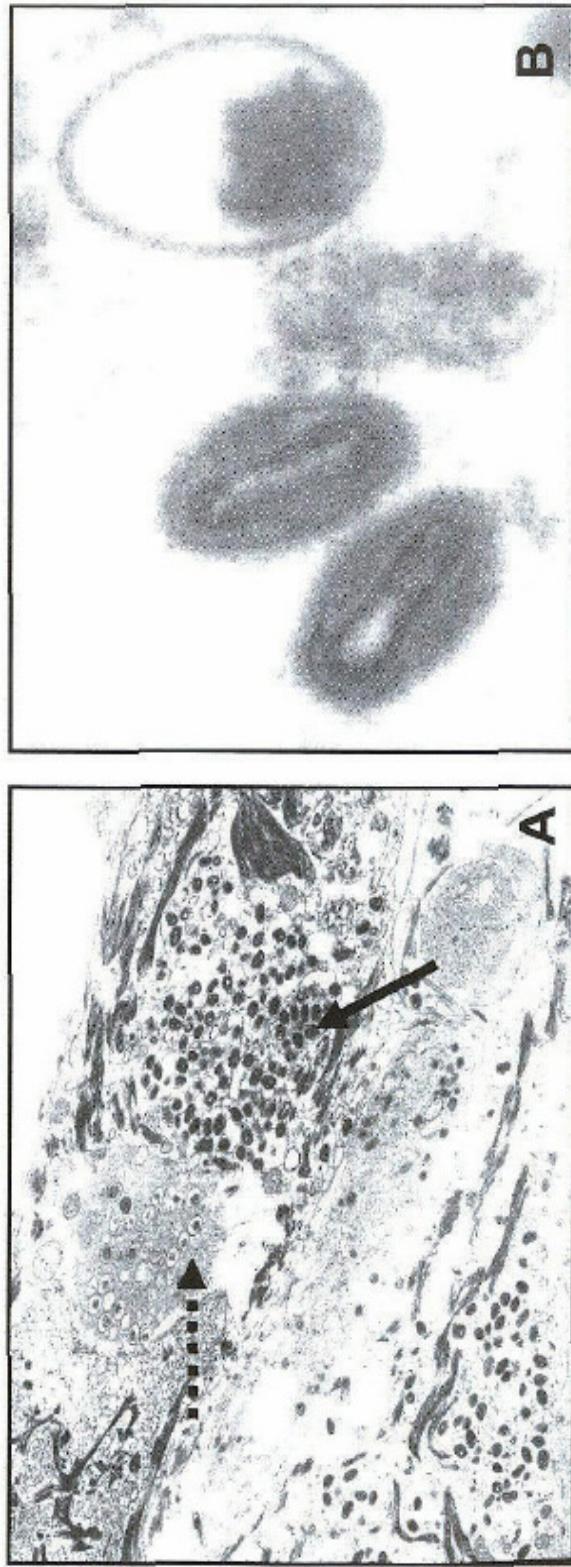


Figure 3. Electron micrograph of a human skin biopsy specimen from a monkeypox virus-infected patient. **A.** Keratinocytes with large numbers of mature virions (solid arrow) and immature virions in the process of assembly (dashed arrow). **B.** At left, there are 2 cross-sections of mature virus particles that have the characteristic dumbbell-shaped inner cores of poxviruses. At right, the slightly larger round object is an immature virus particle that is not fully assembled. Micrographs were kindly provided by Marshfield Clinic, Marshfield, Wisconsin.

Human MPX-Liberia 1971



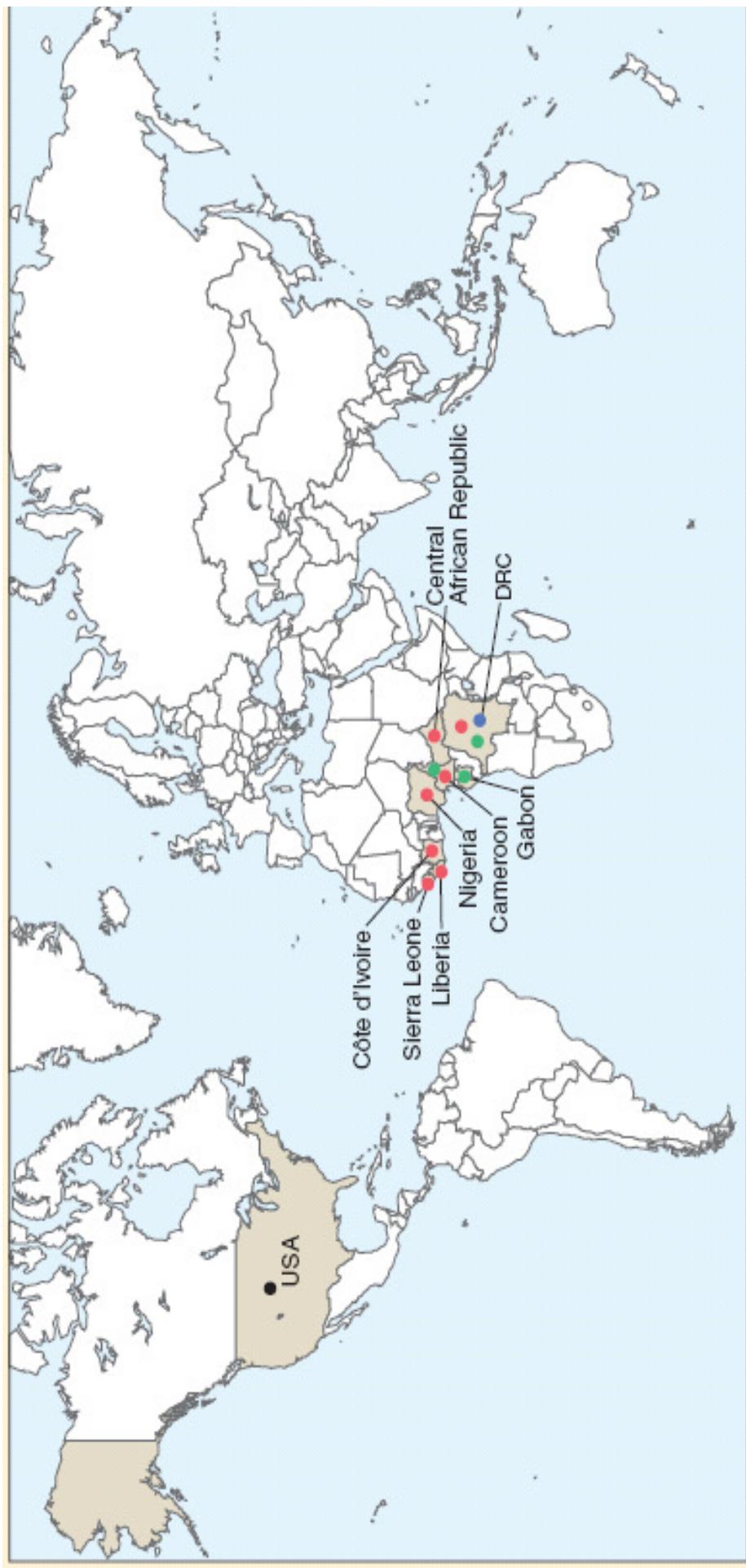
CDC - 1971

MPX Historical Notes

- 1958-Initial discovery
Denmark-Outbreak in laboratory primates
- 1970-First human case identified in Zaire
9 mo child who had not been vaccinated against SPX
- 1970-1994: Following eradication of SPX in sub-Saharan Africa, about 400 cases of MPX were reported from the tropical-forested countries of West and Central Africa
 - 95% of these were recorded in Zaire following intense surveillance from 1982-1986
 - Epidemiologic and laboratory studies during this period provided the foundation of our knowledge about MPX in the natural setting.

Epidemiology of MPX in Africa

- Sporadic viral zoonosis confined to equatorial rain forests of West and Central Africa
 - Natural history is not clear
 - Monkeys, other primates, including humans, are susceptible but are unlikely reservoir hosts
 - Antibody evidence indicates that wild rodents (African tree squirrels, Gambian giant rats, elephant shrews, etc) serve as primary viral reservoirs
 - Routes of exposure and transmission have not been clearly delineated but butchering monkeys and contact with sick primates and rodents are thought to be the primary sources of exposure
 - Increased trade in bush meat is one possible risk factor for outbreaks of human MPX in enzootic areas
- Cases of MPX tend to occur singly or in small clusters.
Human-to-human transmission occurs infrequently



EXPLANATION

Human cases of monkeypox

- 1970–1986
 - Cameroon
 - Central African Republic
 - Côte d'Ivoire (Ivory Coast)
 - Zaire/Democratic Republic of Congo (DRC)
 - Liberia
 - Nigeria
 - Sierra Leone
- 1987–1995
 - Cameroon
 - DRC
 - Gabon
- 1996–1999
 - DRC
- 2000–2004
 - USA
- 2005
 - 2005

Figure B. Geographic distribution of reported human cases of monkeypox from 1970 (first case identified) through 2002.¹⁴⁶

Updated from Friend. MPX- A Lesson Not Yet Learned...; USGS Circular 1285; 2006 p 170.

MPX-suspected wildlife reservoirs

Table B. Suspected wildlife reservoirs for monkeypox virus.

| Species | Comments |
|------------------------|---|
| Squirrels | Considered possible reservoirs in Zaire on the basis of serologic finding and isolation of the virus from one Thomas's tree squirrel; ¹⁴⁷ also implicated in later studies. ¹⁵⁰ |
| Kuhl's tree squirrel | |
| Thomas's tree squirrel | |
| Sun squirrel | |
| Gambian rat | High percentage of human cases during 1996–1997 epidemic involved eating and other exposures to Gambian rats; also 16% of rats tested had antibody to monkeypox virus. ¹⁵⁰ |
| Porcupine | Similar finding to Gambian rat but no live animals sampled. ¹⁵⁰ |

Source: Friend M. Monkeypox-A Lesson Not Yet Learned. In: Disease Emergence and Resurgence: The Wildlife Human Connection. USGS Circular 1285; 2006.

MPX Clinical Illness

Similarities Compared to SPX

- Incubation period: like SPX--12 days (Range 7-17 days)
- Signs and symptoms also similar to smallpox:
 - Fever, HA, myalgias, backache, swollen lymph nodes, general feeling of discomfort and exhaustion, generalized pustular rash
 - Rash resembles the ordinary or modified forms of SPX
 - macules → papules → vesicles → pustules
 - umbilication → scabbing → desquamation
- Differences Compared to SPX
 - Lymphadenopathy tends to be more prominent than in SPX and occurs early in the disease.
 - Routes/mechanisms of p-t-p transmission are similar to those for SPX but secondary transmission in MPX is lower, about 8%.

MPX Clinical Illness

Similarities Compared to SPX

- Illness lasts 2 to 4 weeks

Differences Compared to SPX

- Case fatality ratio for MPX is less compared to SPX
 - Among unvaccinated populations in West Africa, the CFR varies between 1%-10%.
 - It may be higher in children
 - For comparison CFR for SPX is 20-50%

Lymphadenopathy is the principal clinical finding that helps to distinguish monkeypox from smallpox.



Figure 2. *A*, A 3-year-old African boy with monkeypox and axillary lymph node enlargement (arrow). *B*, A 7-year-old African girl with monkeypox and bilateral inguinal lymphadenopathy (arrows). For both patients, lymphadenopathy was the main differential diagnostic criterion that distinguished monkeypox from smallpox. Photographs were kindly provided by Mark Szczepaniowski, World Health Organization. *C*, A 7-year-old girl from Tokondo village, Kasai-Oriental province, Democratic Republic of Congo, with reported exposure to a dead monkey. Note the characteristic pustules on her back. Photograph was taken on 4 October 2004 and kindly provided by Dr. Robert Shongo.

Differential Diagnosis

| | Monkeypox | Smallpox | Chickenpox |
|-------------------------------|--|---------------------------------------|--|
| Incubation Pd | 7-17 days | 7-17 days | 12-14 days |
| Prodrome Pd | 1-4 days | 2-4 days | 0-2 days |
| Fever, severity | Moderate | Severe | Mild or None |
| Malaise, severity | Moderate | Moderate | Mild |
| Headache, severity | Moderate | Severe | Mild |
| Lymphadenopathy | Moderate to severe | None | None |
| Lesion Depth | Superficial to Deep (4-6 mm) Multilocular | Deep (4-6 mm) Multilocular | Superficial (2-4 mm) Unilocular |
| Lesion Distribution | Centrifugal (mainly) | Centrifugal | Centripetal |
| Lesion Stage | Homogenous | Homogenous | Heterogeneous rash |
| Time to desquamation | 14-21 days | 14-21 days | 6-14 days |
| Lesions on palms/soles | Common | Common | Rare |

Is MPX likely to become endemic in the human population?

- MPX virus genome lacks some of the immunomodulatory genes possessed by the SPX virus genome.
- This suggests that MPX is unlikely to become endemic in the human population.

Prevention

- Due to genetic similarities between smallpox and monkeypox, vaccination with *Vaccinia virus* protects against both diseases.

Famous Words

“There is no evidence that monkeypox will become a public health threat outside of enzootic areas.”

Control of Communicable Diseases Manual

APHA, c. 2000

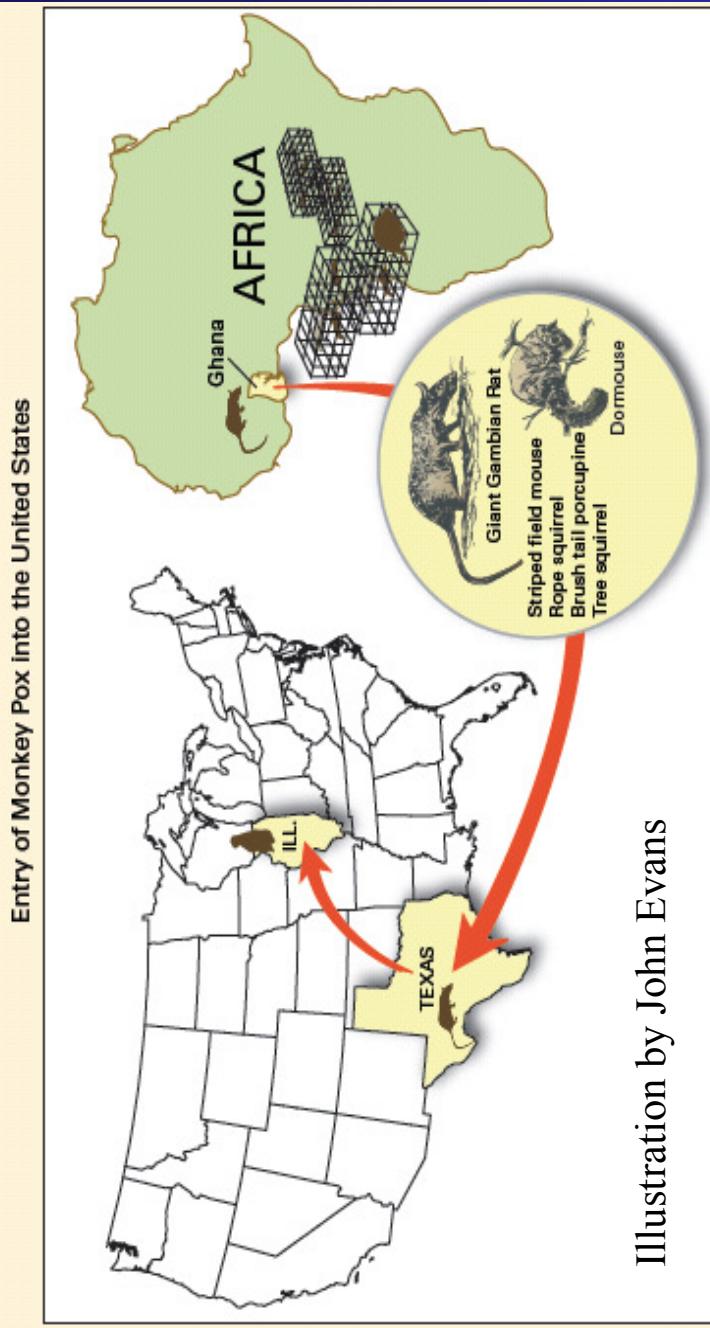
A funny thing happened on the way
to the:

- ?? Forum—No
- ?? Market—No
- ?? Pet store—Yes

West African Rodents

50 Gambian Giant Rats
510 Dormice
53 Rope Squirrels
47 Tree Squirrels
100 Striped Mice
2 Brushtailed porcupines

Imported from
Accra, Ghana to US
April 9, 2003



MPX Human Cases

| | |
|----|----|
| WI | 39 |
| IN | 16 |
| IL | 12 |
| MO | 2 |
| KS | 1 |
| OH | 1 |

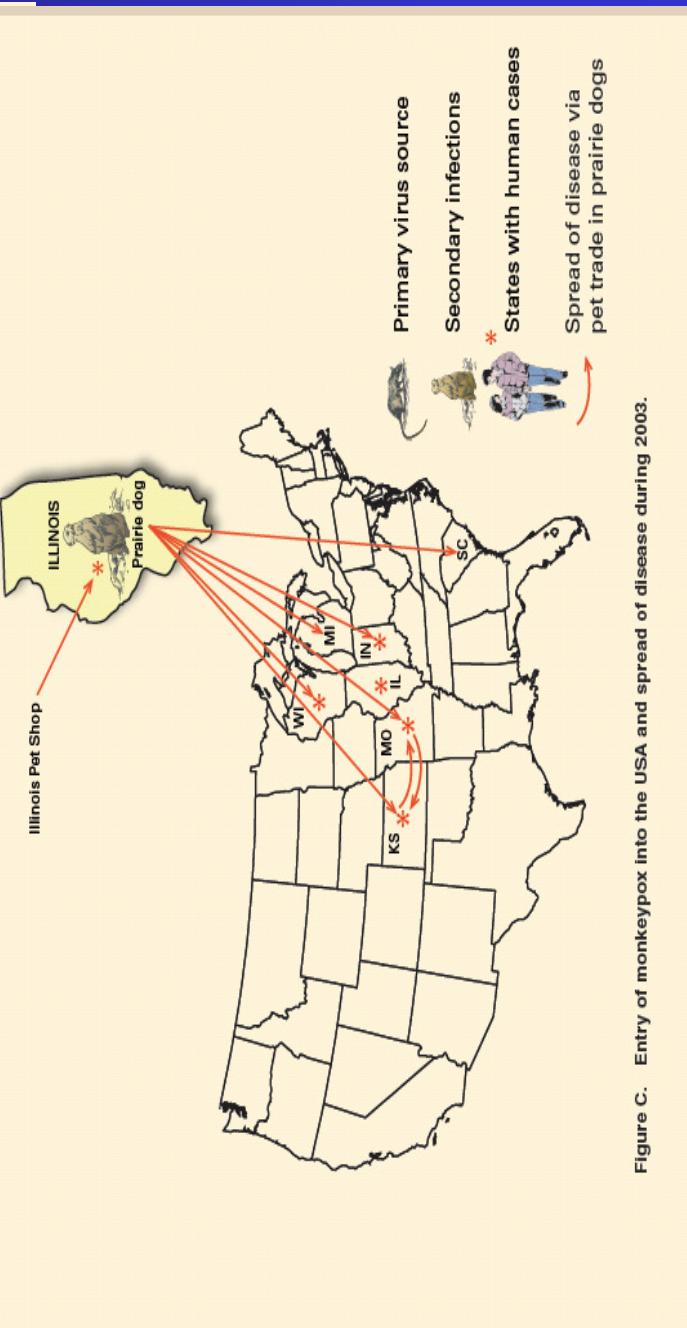


Illustration Source:
Friend M. USGS 2006

2003 MPX Outbreak in US

- First human cases diagnosed in mid and late May in Wisconsin and Illinois
- By July 71 cases in six Midwestern had been reported to CDC
 - Wisconsin 39 Indiana 16 Illinois 12
 - Missouri 2 Kansas 1 Ohio 1
- Classification
 - 35 Laboratory confirmed
 - 36 Suspect or probable

Monkeypox: Signs and Symptoms 2003 US Outbreak-34 Patients

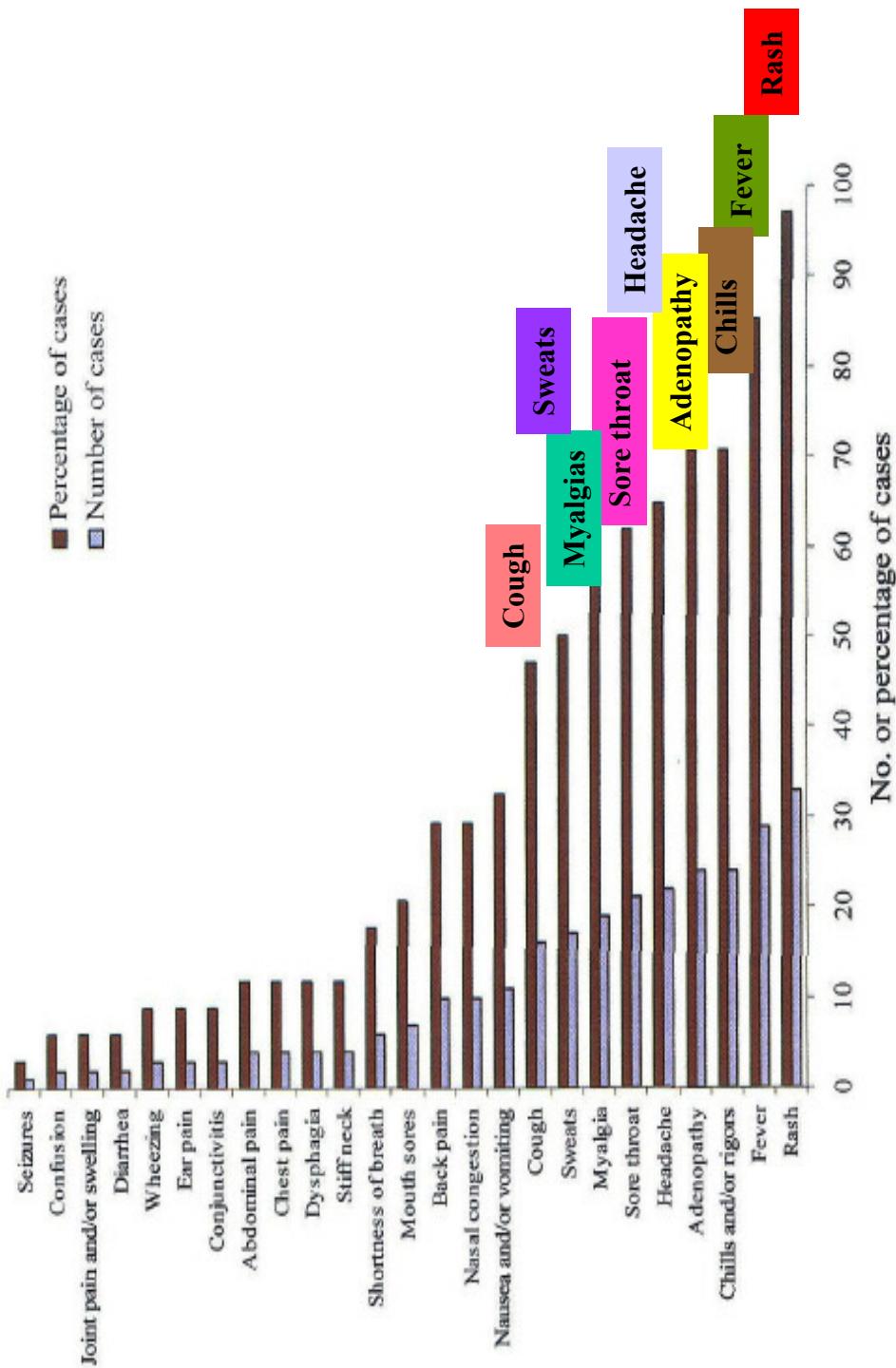


Figure 1. Signs and symptoms for 34 patients with confirmed monkeypox, United States, 2003

Source: Nalca et al. Clinical Infectious Diseases Vol 41 Dec 15, 2005
Symptom highlights to the right added.

Monkeypox Rash in Midwestern US Outbreak Cases

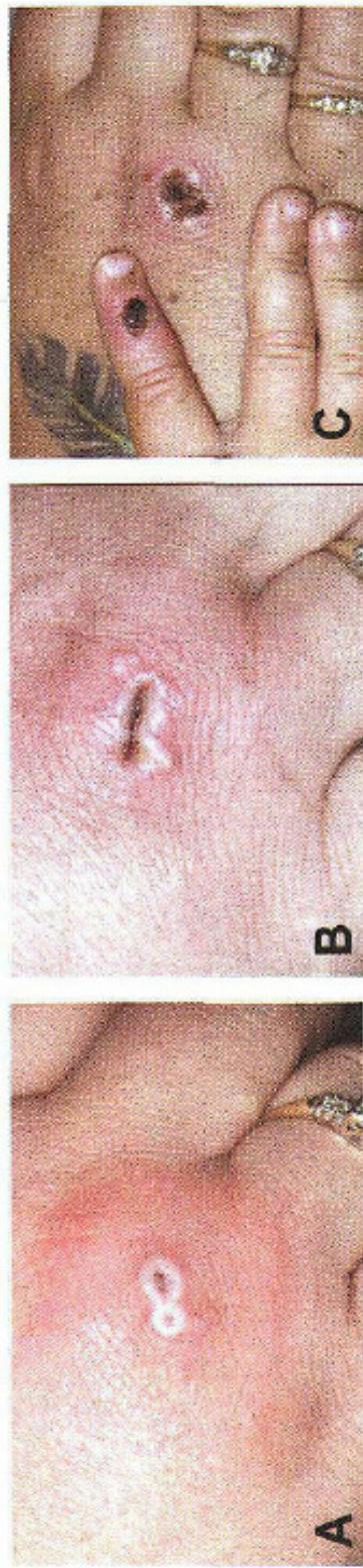


Figure 1. *A*, Vesicle and erythema on the hand of a woman on day 1 of monkeypox virus (MPXV) infection during a US outbreak of monkeypox in 2003. *B*, Satellite vesicles after biopsy on day 3 after MPXV infection. *C*, Crusted primary MPXV infection sites on the hands of a woman (on day 9 after infection) and her child. Photographs were kindly provided by Marshfield Clinic, Marshfield, Wisconsin.

Source: Nalca et al. Clinical Infectious Diseases 2005;41 (15 Dec), 1767.

Hospitalized 10 Year Old Girl with MPX Retropharyngeal Abscess, Tracheal Impingement, and Cervical Lymphadenopathy

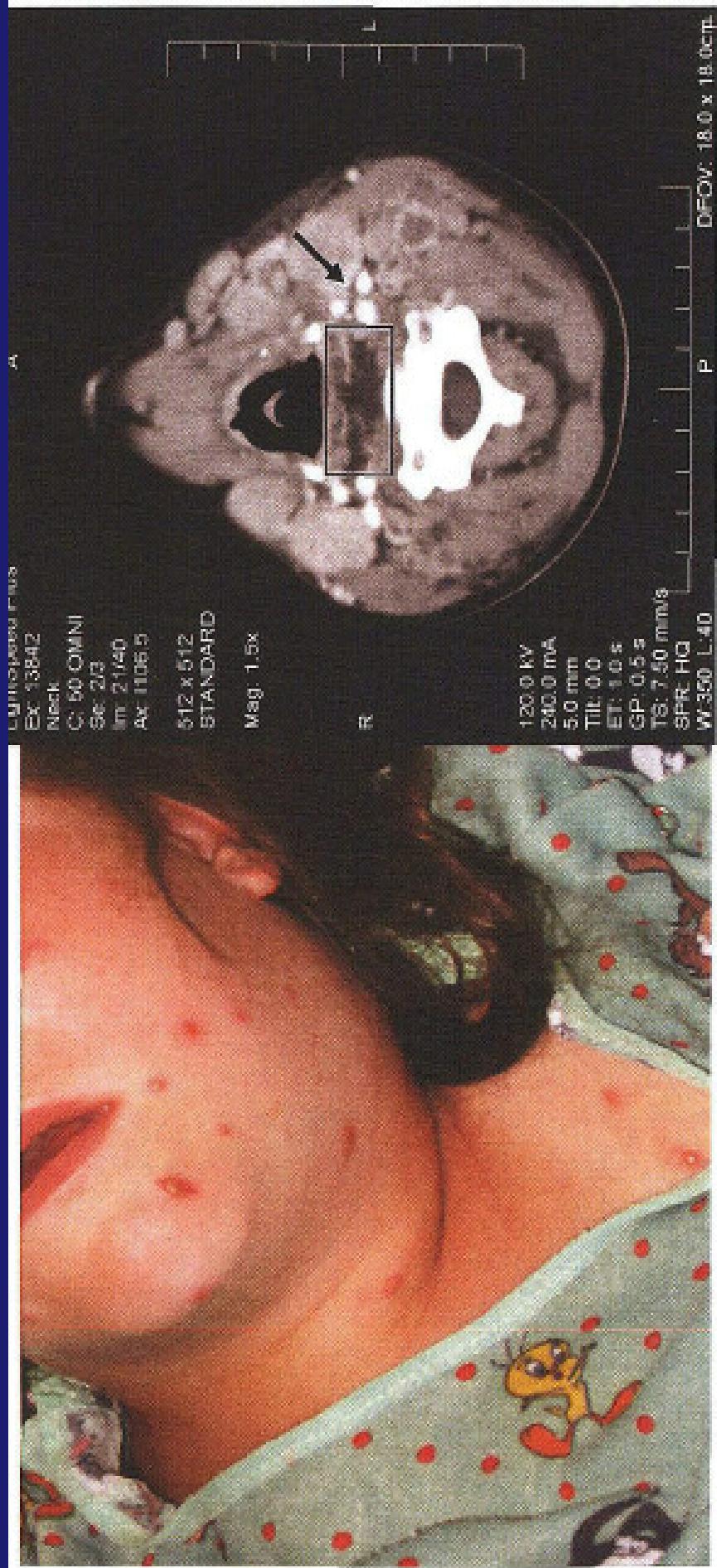


Figure 3. Physical (left) and radiographic (right) characteristics of monkeypox infection for a girl aged 10 years with a retropharyngeal abscess, tracheal impingement, and cervical lymphadenopathy. United States, 2003.

Source: Nalca et al. Clinical Infectious Diseases 2005;41 (15 Dec), 1749.

Human Monkeypox Case Definition

Updated interim definition January 2004

- **Clinical Criteria**

- Rash (macular, papular, vesicular, or pustular; generalized or localized; discrete or confluent)
- Fever (subjective or measured temp of ≥ 99.3 F (37.4 C))
- Other signs and symptoms
 - Chills and/or sweats
 - Headache
 - Backache
 - Lymphadenopathy
 - Sore Throat
 - Cough
 - Shortness of Breath

Human Monkeypox Case Definition

Updated interim definition January 2004

- Epidemiologic Criteria

- Exposure to an exotic or wild mammalian pet obtained on or after April 15, 2003, with clinical signs of illness (e.g., conjunctivitis, respiratory symptoms, and/or rash)
- Exposure to an exotic or wild mammalian pet with or without clinical signs of illness that has been in contact with either a mammalian pet or a human with monkeypox
- Exposure to a suspect, probable, or confirmed case of monkeypox

Human Monkeypox Case Definition

Updated interim definition January 2004

- **Laboratory Criteria**

- Isolation of monkeypox virus in culture
- Demonstration of monkeypox virus DNA by polymerase chain reaction testing of a clinical specimen
- Demonstration of virus morphologically consistent with an orthopoxvirus by electron microscopy in the absence of exposure to another orthopoxvirus
- Demonstration of presence of orthopoxvirus in tissue using immunohistochemical testing methods in the absence of exposure to another orthopoxvirus

Human Monkeypox Case Classification

- **Suspect Case**
 - Meets one of the epidemiologic criteria AND
 - Fever or unexplained rash **AND** two or more other signs or symptoms with onset of first sign or symptom <21 days after last exposure meeting epidemiologic criteria
- **Probable Case**
 - Meets one of the epidemiologic criteria **AND**
 - Fever **AND**
 - Vesicular-pustular rash with onset of first sign or symptom <21 days after last exposure meeting epidemiologic criteria
 - **OR** If rash is present but the type is not described, demonstrates elevated levels of IgM antibodies reactive with orthopox virus between at least days 7 to 56 after rash onset
- **Confirmed Case**
 - Meets one of the laboratory criteria

Human Monkeypox Case Exclusion Criteria

- A case may be excluded as a suspect or probable monkeypox case if:
 - An alternative diagnosis can fully explain the illness, OR
 - The case was reported on the basis of primary or secondary exposure to an exotic or wild mammalian pet or a human (see epidemiologic criteria) subsequently determined not to have monkeypox, provided other possible epidemiologic criteria are not present, OR
 - A case without a rash does not develop a rash within 10 days of onset of clinical symptoms consistent with monkeypox
 - The case is determined to be negative for non-variola generic orthopoxvirus by polymerase chain reaction testing of a well sampled rash lesion by the approved Laboratory Response Network (LRN) protocol.
 - The case is determined to have undetectable levels of IgM antibody during the period of 7-56 days after rash onset.

NC Response

- Active surveillance-febrile rash illness
- Veterinary Public Health
 - Local Health Departments
 - NC Department of Agriculture-regulates Pet Stores
 - Licensed Veterinarians
 - Local Pet Stores-public health issues
 - Individuals with Pets

Prairie Dog with Owner

Animal is healthy

Animal is sick

Take to veterinarian

Order given to euthanize animal

Owner seeks permission from NCDA/LHDept to give to refuge

Animal remains at home of owner

Refuge space available
Refuge space available and
Permission given

Veterinarian examines animal, history, physical & maintains full records

Animal is healthy or doesn't appear to have MPX

Animal is sick & appears to have MPX

DVM notifies LH Dept and NCDA&CS immediately: Does DVM allow owner to keep?

Return animal to owner

Euthanize animal:
Incinerate or freeze according to instructions by LHD or NCDA

Give to refuge, refuge keeps animal on premises, maintains full records, notifies LHD or NCDA if animal sickens, dies, escapes

Prairie Dogs: Most Social Members of the Squirrel Family

Genus *Cynomys*- 5 Species

Black-tailed (*C ludovicianus*) * dry plains central TX to Canada
White-tailed (*C leucurus*)-western US, CO, UT, WY, MT
Gunnison's (*C gunnisoni*)- Four corners 5000-11,000 ft
Utah (*C parvidens*)-smallest, ESA: threatened
Mexican (*C mexicanus*)- ESA: endangered



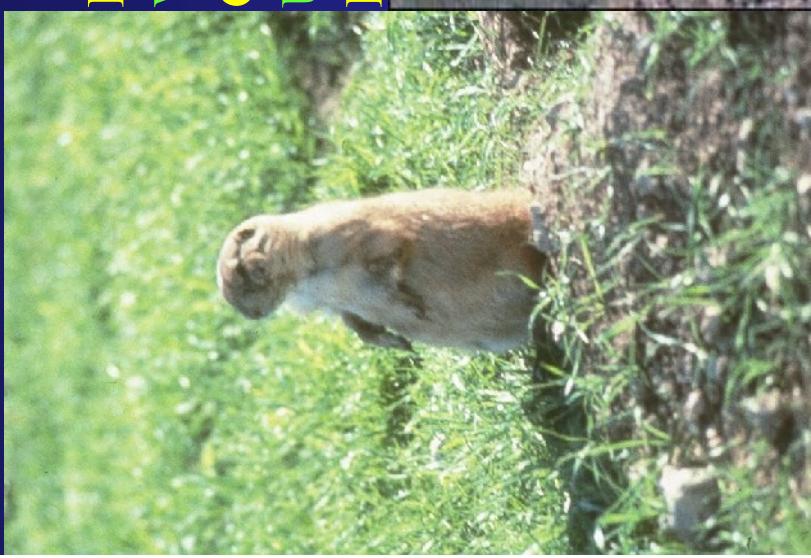
- * Sold in pet stores in US and abroad
- Public Health Risks:
 - Plague from fleas
 - Tularemia (Japan)
 - Salmonellosis



Photos: US Fish & Wildlife Service

In 1900, a prairie dog settlement on the high plains of TX extended 100 by 250 miles with an estimated population of 400 million.

Predators: Hawks, owls, eagles, ravens, coyotes, badgers, ferrets, snakes, and humans



Animals Infected with MPXV

Table A. Animals found to be infected by monkeypox virus. 108, 148, 150

| Captive species ^a | Free-ranging species ^b | Experimental infections |
|------------------------------|-----------------------------------|--------------------------|
| Gorilla | Domestic pig | Laboratory rat |
| Orangutan | Elephant shrew | Laboratory mouse |
| Chimpanzee | Thomas's tree squirrel | Domestic rabbit |
| Cynomolgus monkey | Kuhl's tree squirrel | 13 lined ground squirrel |
| Rhesus monkey | Sun squirrel | Prairie dog |
| African green monkey | Gambian rat | |
| Squirrel monkey | Spot-nosed monkey | |
| Marmoset | Lesser white-nosed guenon | |
| Indian langur | Allan's monkey | |
| Malayan langur | Colobus monkey | |
| Cercopithecus | | |
| Gibbon | | |
| Pigtailed macaque | | |
| Giant anteater | | |
| Prairie dog | | |

^aSpontaneous infections in animals' holdings.

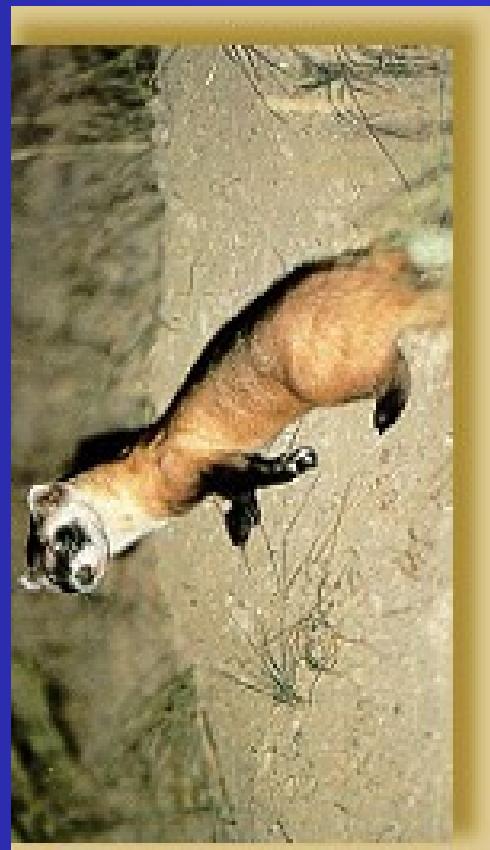
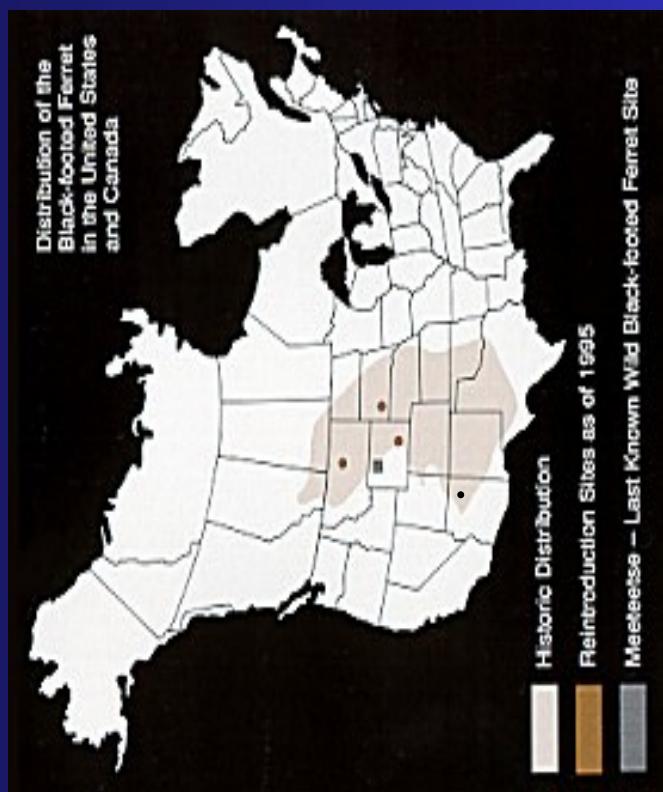
^bAnimals sampled in the wild found to have antibody against monkeypox virus.



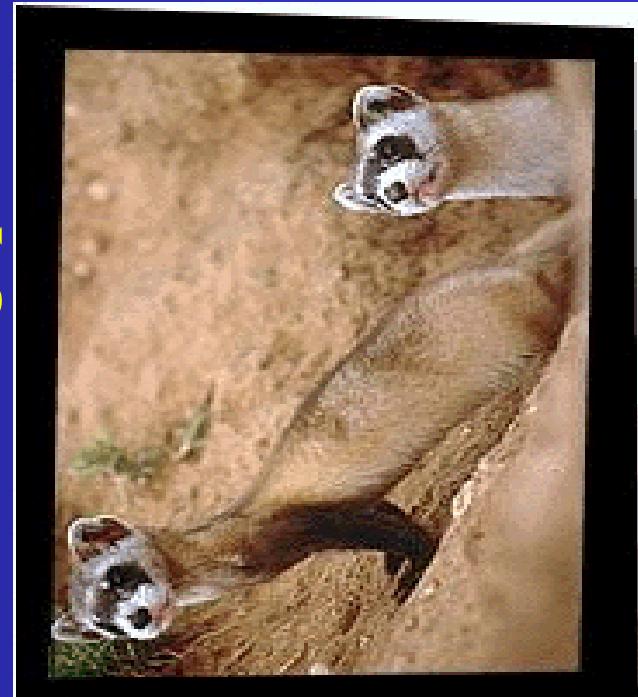
Photo courtesy of U.S. Fish and Wildlife Service

Adapted from : Friend M. Circular Monkeypox-A Lesson Not Yet Learned. In: Disease Emergence and Resurgence: The Wildlife Human Connection. USGS 1285; 2006.

**Black-footed Ferret - important predator of prairie dogs-PDs exterminated
Thought extinct until small colony discovered in 1981 near Meeteetse, Wyoming**



Mustela nigripes



Photos: US Fish and Wildlife Service

North American Black-footed Ferret

One of three ferrets in the world:

European ferret (European polecat) (*Mustela putorius*)

Domesticated (*Mustela putorius furo*)

Pets

Led to Discovery of Influenza Virus

Animal Model for Influenza

North American black-footed ferret (*Mustela nigripes*)

Fossil evidence indicates it is descended from the Siberian ferret which crossed into NA during the Pleistocene Period

Siberian ferret (Steppe polecat) (*Mustela eversmannii*)

closest relative of BFF

Black-footed Ferret Facts

- 1967 Listed as federally endangered species, thought to be extinct
- 1981 Small population discovered by a rancher near Meeteetse, WY
- 1984 Estimated population of 129 crashed due to canine distemper-no immunity
- 1985 Six ferrets in the Meeteetse population were captured and moved to captive breeding facilities at the WY Game and Fish Department's Sybille Research Facility-all died from canine distemper
- 1987 Remaining 18 ferrets captured - Initial breeding efforts unsuccessful
 - 1988 Breeding success
 - 1992 Reintroduction to the wild
- 1998 SSP captive breeding facilities 425 born with 321 kits surviving
- 2006 Wild population now approx 700-850 in five western states
 - BFF live in Prairie Dog burrows 90 % BFF diet is PD
 - Single ferret family requires 100 acres of PD colony for sustenance
- Threats to wild BFF population:
 - Loss of prairie dog habitat
 - Predators
 - Disease (canine distemper, plague**, influenza)
 - MPX if captive prairie dogs infected with MPX were released into wild
- Threats to captive BFF population (VA, KY, WY, AZ, CO, Canada):
 - Disease as above and MPX if MPX-infected prairie dogs were fed to ferrets

What good are Gambian giant rats, anyway?



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Wines M. For Sniffing Out Land Mines, A Platoon of Twitching Noses. *The New York Times* May 18, 2004.
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 - <http://www.cdc.gov/ncidod/monkeypox/factsheet.htm>
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 - <http://www.cdc.gov/ncidod/monkeypox/autopsy.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/labbiosafetyguide.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/speciemenguide.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/specimentrackingform.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/infectioncontrol.htm>
 - <http://edocket.access.gpo.gov/2003/03-27557.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/law.htm>
 - <http://www.cdc.gov/ncidod/monkeypox/pet.htm>